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Medical Surveillance of Exposed Persons After Exposure to PCBs, Chlorinated Dibenzodioxins and Dibenzofurans after PCB Transformer or Capacitor Incidents

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The panel discussion from the perspective of occupational medicine regarding appropriate medical surveillance after a PCB transformer or capacitor incident is reviewed. A thorough occupational medicine history and physical examination is stressed for any worker or other patient who may have been exposed. Appropriate laboratory tests, including complete blood count with differential, serum chemistries, serial blood PCB determiniations, fat biopsy to estimate furan and dioxin levels, if indicated, pulmonary function tests, chest X-rays, urinalysis including porphyrin measurement, nerve conduction velocity testing and other tests are discussed. No consensus was reached on recommended length of medical followup.

Because the field is rapidly changing, yearly updates of medical protocols are warranted. In addition, the need for surveillance to be conducted by specialists with training and experience in the fields of occupational medicine and nursing was emphasized. It was stressed that measuring the chemicals and their levels in soot and air and then comparing these with the patient's blood or fat levels, in the case of PCBs, furans and dioxins, is vital. It was noted that at present no modality of treatment is known to be clinically efficacious in removing PCBs, furans and dioxins from tissues or blood.

Introduction

The occupational medicine physician is faced with a dilemma after PCB, dioxin or furan and chlorinated benzene incidents (*1,2*). Frequently no baseline data is available for exposed workers. Next, there are few if any toxicological data on the various isomers which may exist in the soot or air for animals let alone humans. There are no standard assays yet for determining or estimating exposure. Certainly, based on animal data and limited but growing human data there is no standard approach which is accepted by most experts in the field.

However, based on animal toxicological data from multiple species, human data from various PCB exposed workers, and data from a number of incidents, the Yusho and Yu Cheng PCB/furan incidents in the Orient, the Seveso, Italy, dioxin incident, and the Nitro, West Virginia Monsanto dioxin incident as well as the more recent Binghamton State Office Building (BSOB) incident it seems reasonable to consider the following approach based on the limited medical data available at this time.

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Laboratory Data

First, one would wish to immediately draw a fasting blood sample from the patient as soon after the incident as possible to attempt to obtain baseline data. In addition, urine specimens for routine urinalysis as well as possibly for urine porphyrin levels and patterns should be obtained. Blood samples for hemoglobin, hematocrit, white and red cell counts as well as differential and platelet count should be performed. The usual blood chemistries, especially all liver tests, such as SGOT, SGPT, gamma GTP, alkaline phosphatase, direct and indirect bilirubin, and serum cholesterol and triglyceride levels, as well as albumin and globulin levels should be obtained. Several samples of serum, not drawn in plastic syringes or containers should be frozen for possible future PCB levels and pattern analysis. Blood, 10 to 100 mL, should also be drawn and frozen for possible future dioxin and furan analysis. Urinary glucaric acid and urinary 6-*b*-hydroxycortisol as indicators of microsomal enzyme induction may also be useful; for the same reason, some authors recommend the aminopyrene breath test (*3–6*).

Examination of lymphocytes for immune competance is not usually performed, although Bekesi (*7*) at Mt. Sinai in New York and Carnow (*8*) in Chicago have reported immune deficiency in humans after exposure

to dioxins (along with other chemical contaminants). Carnow and associates also perform sperm analysis, having found sperm abnormalities in a number of patients, after one incident.

Thymus and bone marrow may be of interest, especially in the young. Bone marrow activity is customarily monitored by hematological screening, although bone marrow aspiration might be indicated or at least not contraindicated were there to be abnormal findings. In a similar fashion, based on the findings of Hay (*9*) that 2,3,7,8-TCDD is mutagenic in at least one cell system and considering that these compounds may well be promoters if not inducers of cancer in humans, leading to chromosomal alterations, it may be reasonable to consider peripheral lymphocyte chromosome studies as a possible biological marker. This appears not yet to have been systematically studied carefully by experts in the field after such chemical exposure in humans.

Parenthetically, because of multimillion dollar legal verdicts after exposure to dioxin and other chemicals, it may prove better to perform unusual and costly tests for legal as well as medical reasons sequentially during the first few months after exposure to detect pathological changes which might arise from the incident—or to rule out such changes.

Radiographic studies of lungs seems indicated to establish a baseline, as do pulmonary function tests because of compromises in pulmonary function reported by Warshaw and colleagues after PCB exposure (*10*). From monkey data one wonders whether an upper gastrointestinal (GI) series might not be indicated to detect or rule out changes in gastric mucosa. Gastroscopy might also be appropriate, especially if symptoms are present after exposure. X-rays with the use of contrast media might be of selective interest, as might computerized axial tomography (CAT scans) to evaluate liver or spleen. PET scans or NMR evaluations may prove useful in future years especially to provide early warning of functional organ change but have not thus far been utilized in follow up of PCB or dioxin exposed patients, to the best of our knowledge.

Fat biopsies are the only means available at present to measure furan or dioxin levels in body tissue and are thus, in our opinion, indicated as a biological marker to estimate extent of exposure. For the same reason, liver ultrastructural changes have been reported in multiple animal species as well as in man after PCB, dioxin, chlordecone and related chlorinated aromatic compounds and therefore biopsies may also be indicated as biological markers, especially if liver pathology consistent with the chemical exposure exists.

Medical History

A thorough medical history should be taken, including all possible chemical exposures, alcohol, medication and illicit drug use, previous illness and familial illness, allergies and reproductive outcomes in family members as well as cancer history. In short, it must be a thorough occupational history taken by a knowledgeable and experienced occupational medicine physician.

Medical Examination

The examination of the patient should include color photographs of skin including face, shoulders, chest and back, at least, in order to establish baselines. Photography of the entire body is desirable. At the present time, chloracne is rarely observed after dioxin or PCB exposure, and its diagnosis varies from physician to physician, with widely differing criteria being used (*11–13*). Any acne appearing in an adult who did not have acne before exposure to a chloracne producing compound is, by definition, chloracne, in the judgment of some physicians. Others may require a group of workers to develop skin lesions after exposure to a "chloracnogen" before feeling comfortable classifying lesions as chloracne. Still others may elect to perform a skin biopsy to diagnose hyperkeratosis and atrophy of sebaceous glands microscopically before designating a lesion as chloracne. Other skin lesions, such as transient erythema, may also arise from such exposure. This provides useful documentation of exposure and sensitivity to such chemicals; photographs of such transient lesions provide documentation afterwards.

Next, a careful examination of the eyes is indicated, remembering the Yusho patients and their conjunctivitis and discharge (*14,15*). Staining of gingiva may be found after exposure to PCBs and furans, again as seen in Yusho. Discolored skin and nails appears to predominate in newborns where there was transplacental transfer of these compounds from mother to baby while still in utero.

Moving to the chest, careful evaluation of the lungs is indicated. Serial pulmonary function tests might be expected to reveal damage or lack of damage from these compounds better than auscultation and percussion (*10*). Wheezing or signs or symptoms of edema might be noted with an immediate allergic response, especially from chemicals which might accompany the dioxins, furans and PCBs. A pulmonary function test might be repeated one and two years after initial exposure to detect latent damage or recovery. One recalls the asbestos-induced mesiotheliomas with peak incidence 30 to 40 years after first exposure to asbestos (*16*). Possibly, repetition at least once a year of major screening tests might be indicated until more medical data becomes available concerning possible toxic effects of these chemicals alone and in combination in humans. Pulmonary function abnormalities have been described in Yusho, as have excess pulmonary secretions.

Cardiac problems other than increased blood pressure (*17*) have not yet been described so only routine cardiovascular evaluation of heart and blood pressure seems indicated. The increase in serum cholesterol and triglycerides suggest a careful monitoring for atheromatous blood vessel compromise considering especially

coronary arteries, cerebral blood vessels and, possibly, abdominal aorta.

Since renal infection and hemorrhage have been described following dioxin exposure by Kimbrough and others, careful attention to costovertebral angle tenderness is indicated. Levels of urinary uro- and coproporphyrins and their ratios should also be considered (*18*) but are usually not abnormal after dioxin, chlorinated phenol, phenoxy herbicide or PCB exposure.

Because the liver has been found to be a target organ for dioxin pathology in all species studied (*19*), careful evaluation of the liver is important. The presence or absence of tenderness or enlargement, as noted by palpation and percussion, should be noted. Usually abdominal findings are not remarkable but are of use in establishing a baseline; one would not expect immediate pathological findings since dioxins and PCBs are known for their delayed action in most animal species. The liver can best be monitored by serum enzyme elevation and liver biopsy with electron microscopic analysis of tissue where relatively characteristic lesions occur after dioxin, PCB, or Kepone exposure. Aryl hydroxyl hydroxylase (AHH) or cytochrome P448 induction would be useful to follow after exposure but there appears to be no practical way to monitor this directly in humans at present. Guzelian (*3*) has pointed out the pitfalls of relying on enzyme levels alone and has also eloquently illustrated the value of electron microscopy when analyzing liver needle biopsies (*20*). Without ultrastructural analysis, important and possibly characteristic or pathegnomonic lesions may be missed. Therefore, when liver biopsies are taken, which may well be indicated after dioxin exposure much more frequently than they are done at present, ultrastructural evaluation is essential. Alterations in liver ultrastructure, while similar with many chlorinated comounds, may prove sensitive, although these are not specific or pathognomonic lesions.

Continuing with the abdominal evaluation, palpation and percussion of the spleen, to evaluate tenderness or increase in size is theoretically indicated because of the frequency of involvement of immune, lymphatic, or reticuloendothelial systems in multiple animal species (*19*). However, the human literature is not replete with positive findings here either. It is not certain whether this is because humans are less susceptible to the toxic effects of these drugs than the more susceptable animal species or whether careful clinical evaluation has not yet been carried out or reported after the now increasingly frequent PCB exposures.

Continuing the physical examination, careful examination of the penis and also testes is indicated in males. Penile abnormalities have been reported by Carnow in a series of railroad workers in a recent court case (*8*). Since etiology is important for legal as well as medical reasons, careful recording of any abnormalities existing shortly after or ideally, before, may be of great medical and legal usefulness. Again, because of these chemicals' usual latency, penile deformity would not be expected to be found immediately after such incidents. Examination of testes seems indicated because of the teratogenetic properties of these compounds as well as the atropic changes, necrosis and other pathological lesions seen in various species of animals after exposure to dioxins (*19*). Possible adverse reproductive outcome in males exposed to dioxins in the absence of exposure of the females has not been observed in animals. Agent Orange, containing dioxins, is nevertheless suspected by some (*21*) of causing fetal malformations and spontaneous abortions.

For similar reasons, thorough examination of the female reproductive system, including pelvic examination, Pap smear, and breast examination, seems equally indicated after exposure and periodically thereafter, on the assumption that dioxins may well be cancer promoting or inducing compounds in humans and that early detection of cancers of the reproductive tract may well lead to decreased mortality and morbidity.

Neurologial examination after dioxin exposure has usually focussed on defects in peripheral nerve conduction velocity. Recently Schaumberg (*22*) has suggested, because of the difficulty in standardizing peripheral nerve conduction tests and because of their discomfort to patients, that peripheral nerve, e.g., finger, vibratory response be the preferred test to detect early subtle pathology in the peripheral nervous system caused by toxic chemicals. This is a topic which occupational medicine physicians and neurologists will no doubt debate for some time. In the meantime, careful documentation of possible nerve damage is essential. Again, this should be followed over time for at least one year, to detect damage occurring after a latent period. Certainly, toxicity of related compounds, such as hexachlorophene and its contaminants, to human brain is known, with brain damage leading to death in some neonates washed in hexachlorophene, and should alert the physician to perform a careful neurologic examination (*23,24*).

Careful attention should also be given to a careful neuropsychiatric history because at this time the neurotoxicologic and neurobehavioral characteristics of most of these chemicals has not been established. It would seem unwise at this time to dismiss complaints of anxiety, fatigue, irritability, inability to sleep, paranoia, impotency, etc., out of hand in patients exposed to dioxins and related compounds. Whether there is a direct toxic effect or not on the central nervous system, there may well be psychogenic pathology regardless of mechanism of action which may lead to death, as was documented by the "successful" suicide of a janitor involved in the Binghamton State Office Building cleanup.

The endocrine system has not been systematically considered in humans after exposure to dioxins, PCBs and related chemicals. Adrenal cortical or medullary changes may or may not occur. Thyroid and pituitary hormone response has likewise not yet been the subject of systematic observation in humans. Ordering specific tests of endocrine function is not contraindicated, but we have no standard protocols to follow at this time. Attention should of course be paid to monitoring en-

docrine abnormalities during physical examination as well as by a careful medical history and by selected laboratory testing.

Treatment of Patients

Careful monitoring of patients, by a physician and nurse knowledgeable in the possible toxicology of the chemicals involved and who are each trusted by the patient and his or her family, is essential. This should take place at least twice a year, preferably, briefly at least, four times a year for the first few years after the incident, because of the rapidly expanding state of our knowledge regarding these chemicals, their possible very toxic effects, the latency period characteristic of these patients and the reassurance it may provide a patient and family to have the same knowledgeable, caring physician and nurse available over a period of years. This surveillance should be lifelong, because of the possibility of cancer or other serious medical problems arising at some future date. Classically in occupational medicine it is common to illustrate the need for lifelong medical surveillance, with its hope of reducing morbidity and mortality by early intervention, by referring to asbestos exposure, where peak mesothelioma rate occurs 30 to 40 years after first exposure. Even in the case of early detection of those cancers for which there is currently no effective treatment, this allows time for the family involved to make social, legal and economic changes in a timely fashion to diminish the impact of a premature death on family members. In addition, early detection may lead to cure. Cancers for which there are no cures today, as, for example, certain of the soft tissues sarcomas believed by some to be caused by dioxins (*25*), may be curable in the future.

Reassurance may be provided to many patients because liver biopsies, fat biopsies or serum data may suggest little or no exposure to toxic chemicals from a given incident. By attempting to quantify additional risk from these chemicals or compare this risk to other, more common risks, it is also possible to reassure some patients.

Reproductive counseling would be another useful function of the medical surveillance program. Certain couples may wish to obtain information regarding the possible adverse effect of PCBs or dioxins and furans on reproductive outcome and plan future child bearing accordingly. In a related matter, because PCBs and related compounds concentrate in breast milk (as well as pass through the human placenta) questions of breast feeding by the exposed mother arise (*26–29*).

Unfortunately, we have no good advice to give nursing mothers regarding unsafe levels of PCBs in breast milk. We also are not certain about the levels of PCBs found in substitutes for mothers milk. In addition we have no data at this time regarding the presence of chlorinated furans or dioxins in human breast milk, as well as regarding their possible or presumed toxic effects on newborns. Yusho babies appear to have suffered toxic effects, including low birth weight, discolored skin and, in some cases death, from maternal PCB and PCDF exposure.

One question the occupational medicine physician is asked frequently by exposed workers and their families is whether the compounds can be removed from the body, especially if they are found by direct measurement in fat or blood, or indirect measures of exposure and sensitivity, such as elevated liver enzymes or skin changes, etc., to be in the exposed worker.

In theory, the answer to this question is affirmative. Nursing mothers certainly excrete PCBs and related fat soluble chemicals in their milk; presumably this could be extended artificially long enough at least to deplete PCB body burden in women. In addition we know from work with chlordecone (Kepone) that one can remove other related chlorinated aromatics from humans.

Starvation type diets were reported at the 1983 National Institute on Environmental Health Sciences North Carolina PCB meeting as being used in the Orient after the Yu Cheng or Yusho incidents where PCBs and furans were consumed. At the 1983 Helsinki PCB meeting, feeding of charcoal to PCB and PCDF exposed workers in an attempt to eliminate some of the toxic chemicals via feces was discussed by Järvisalo, a Finnish occupational medicine physician (*30*). At the present time there appears to be no solid evidence that these methods are of demonstrated efficacy. Obviously that should not preclude conducting tightly controlled clinical trials to ascertain efficacy and potential side effects of special diets, or feeding. Recently, a pharmaceutical product was introduced for clinical testing in humans to attempt to decrease body burden of these compounds. This protocol is currently under investigation in human clinical trials.

It is important to recognize that the attending occupational medicine physician is concerned not only with the level of exposure, as revealed by serum PCB levels or adipose tissue dioxin and furan levels, and patterns of isomers as well, but also the sensitivity of the body to these compounds, as shown by elevated liver enzymes, abnormal liver hepatic parenchymal cell ultrastructure, or rarely, by skin manifestations, including skin cancer, transient erythema or the rarely seen chloracne. Unfortunately at this time we have no sensitivity testing to determine genetic predisposition to react to these compounds. Even our most sensitive tests of exposure, fat biopsies and serum levels, are not well developed at present. We do not know half lives, metabolites, tissues of deposition, routes of bodily elimination to say nothing of toxicity for humans with respect to the majority of polychlorinated dioxin, furan, biphenylene, napthalene, biphenyl ethers or PCB isomers in humans. Remembering the work of Brandt (*31,32*), it is clear that various PCB isomers and metabolites migrate to lung or kidney or liver or adipose tissue. Fachetti's work (*33*) suggests 2,3,7,8-TCDD accumulates in highest concentration in adipose tissue, then liver, and then other tissues at lesser amounts—

at least in one patient who died of pancreatic cancer 5 months after initial exposure and who may therefore not be typical. Rappe (*34*) and also Masuda (*35–38*) in analysis of selected organs from human autopsy tissue after exposure show that various PCB and furan isomers may be found in differing amounts in different organs. Hence, potential toxic effects may vary in a qualitative and quantitative fashion depending on the isomers involved. Thus careful, lifelong surveillance seems indicated for exposed patients at this stage in the evolution of our medical knowledge regarding the effects of these chemicals in humans.

With the rapidly growing experience with human exposure to dioxins, PCBs and furans, yearly reassessment of appropriate medical surveillance is indicated. New findings of high levels of dioxins and furans in control patients as well as potentially exposed patients suggests that a lesser degree of medical surveillance is required if there is no evidence of intake of these chemicals after an incident and a greater degree of surveillance is recommended if there is evidence of increased body burden (*39,40*).

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